Depression Formulary Guidance [v2.1]
(adapted from NICE guidelines CG28 and CG90)

1. Introduction

These Guidelines are intended for routine use. However there will be instances where they are not suitable for the patient you are managing, where more bespoke treatment will be necessary. In such instances the rationale for prescribing away from formulary must be recorded.

NICE guidelines suggest the following stepped care model

Focus of the intervention		Nature of the intervention
Step 1	All known and suspected presentations of depression	Assessment, support, psychoeducation, active monitoring and referral for further assessment and interventions
Step 2	Persistent subthreshold depressive symptoms; mild to moderate depression	Low-intensity psychological and psychosocial interventions, medication and referral for further assessment and interventions
Step 3	Persistent subthreshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions; moderate and severe depression	Medication, high intensity psychological interventions, combined treatments, collaborative care and referral for further assessment and interventions
Step 4	Severe and complex depression, risk to life and self-neglect	Medication, high-intensity psychological interventions, electroconvulsive therapy, crisis service, combined treatments, multiprofessional and inpatient care

2. Prescribing and Use of Antidepressants – Key Points

- Prescribing of antidepressants should always be seen as part of a package of care for the treatment of patients with depression and should never be carried out in isolation.
- Do not use antidepressants routinely to treat persistent sub-threshold depressive symptoms or mild depression because the risk-benefit ratio is poor, however they should be considered for people with:
    - A past history of moderate or severe depression or
    - Initial presentation of sub-threshold depressive symptoms that have been present for a long period (typically at least 2 years) or
    - Sub-threshold depressive symptoms or mild depression that persist(s) after other interventions
    - Mild depression that complicates the care of a chronic physical health
    - problem
- Antidepressants should be considered for people presenting with moderate depression.
- Antidepressants should be considered for people with a chronic physical health problem and presenting with moderate depression, after other interventions have been attempted or rejected by the person.
- Antidepressants should be considered for people presenting with severe depression.
- Diagnosis should be carried out using ICD10.
- Antidepressants should be given for 3-4 weeks – if there is no response then the drug should be either escalated to a higher dose, within the recommended range, or if following discussion with the patient, or the maximal dose has been reached should be changed. If there is a partial response then continue for 2-4 weeks, then reassess.
- There is little evidence of difference in efficacy between different drugs but there are differences in side effect profiles; potential for interactions and safety in overdose. If all of

these are equal then cost should be taken in to account.

- The physical health and comorbid conditions/medication should be taken in to account when choosing medication.
- There may be a delay of up to 2 to 4 weeks before onset of antidepressant effect, patients must be made aware that they may get side effects before any benefits are felt, this may be longer in elderly patients
- There is a possibility of increased anxiety, agitation and suicidal ideation in the first few weeks of antidepressant treatment, especially SSRI's and related. If this occurs and is intolerable the judicious use of a benzodiazepine can be considered, as well as increased levels of support, and patient education around this time.
- Discuss antidepressant treatment choice, side effects and adherence with the patient and provide them with written information, or other suitable forms, eg patient information leaflet.
- Patients should be reviewed on a regular basis for continued efficacy and tolerability, ideally no less than 6 monthly.
- For patients with a first episode treatment should be continued for a minimum for 6 months post remission, for those with two or more episodes in a short space of time then 2 years treatment is advised. If patients have multiple relapses then long term treatment should be considered.

3. Side-effects and Interactions

(See table for comparison of common side effects)

Most side effects are transient in nature, and patients should be encouraged to see if they can work through them until they abate.
SSRIs are better tolerated and safer in overdose than other antidepressants.

Common side effects of SSRIs:

- headache, nausea, and anxiety/agitation, especially when starting treatment, this usually settles within the first week or so.
- Other side effects are insomnia, tremor, akathisia, sweating, parathesia, sexual dysfunction, (including reduced libido, and difficulty with erection and orgasm) muscle/joint pain, weight gain (mild), and rarely manic or psychotic symptoms. Citalopram and escitalopram have dose related QTc changes

Common side effects of Tricyclic antidepressants:

- Common side effects tricyclics include anxiety, drowsiness, dizziness, agitation, confusion, anticholinergic effects (dry mouth, constipation, urinary retention, blurred vision); cardiovascular effects (hypotension, tachycardia, arrhythmias and other ECG changes – baseline ECG advised, where appropriate); hepatic effects, changes in blood sugar, increased appetite, weight gain and sexual dysfunction can occur.
- TCAs have similar efficacy to SSRIs but are more likely to be discontinued because of side effects, and are toxic in overdose.

Mirtazapine has few antimuscarinic effects, but causes sedation during initial treatment and is associated with weight gain and blood dyscrasias

Venlafaxine and Duloxetine have similar side effects to SSRI's but can also increase heart rate and blood pressure, as such it is important to identify risk factors prior to prescribing, e.g. uncontrolled hypertension

4. Warnings

- Antidepressants are associated with an initial worsening of anxiety/agitation and an increased of suicidal thinking and behaviour. Monitor closely, at a minimum of two weekly intervals, especially at the start of treatment and when the dose is changed. Consider increased levels of support, and patient education around this time.
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- Abrupt discontinuation (sometimes reduced or missed doses) of antidepressants can lead

to a withdrawal syndrome. Symptoms can include:
    - Dizziness
    - Numbness
    - Tingling
    - Gastrointestinal disturbance
    - Headaches
    - Sweating
    - Anxiety
    - Sleep problems
- Gradual discontinuation over a period of 4 weeks is recommended, if unsure refer to SPC or ask advice from the pharmacy department
- Use antidepressants with care in glaucoma, bipolar, prostate hypertrophy, bleeding disorders and seizures.
- Hyponatremia has been associated with all antidepressants and should be considered in all those who develop drowsiness, confusion, or convulsions whilst taking antidepressants. SSRI's are particularly well known for this and Mirtazapine may be a reasonable alternative should this occur.
- SSRIs can increase risk of bleeding. Caution is required in older adults and when used in combination with NSAIDS, aspirin, valproate or anticoagulants.
- SSRIs can increase risk of falls and osteoporotic fractures in people over 50 years.
- Serotonin syndrome can occur with serotonergic drugs, especially when combined together
- It can present as:
    - Agitation
    - Confusion
    - Tremor
    - Hyperflexia
    - Myoclonus
    - Hyperthermia
- Examples of other serotonergic drugs include: Tramadol, Triptans, Lithium, be mindful of co-prescribing these agents.
- Although no specific ongoing physical health monitoring is required for prescribing antidepressants, this should form part of the overall management of the patient.

5. Special Populations

5.1 Children (under 18 years)

The Nice clinical guideline 28 covers
Using antidepressants in children and young people in the management of depression
This guideline covers children and young people up to their 18th birthday.

The major points are

- Medication should not be prescribed for mild depression.
- First line treatment for moderate to severe depression in children and young people is psychological therapies including:
    - information and advice on self-help materials or strategies, exercise, sleep hygiene, anxiety management and nutrition
- Do not offer antidepressant medication except in combination with a concurrent psychological therapy.
- If psychological therapies are declined medication may still be offered but monitor regularly and focus on adverse drug reactions.
- Fluoxetine is the only antidepressant for which trials in young people show that benefit outweighs risk.
    - The effectiveness in children is not established.
    - It should only be prescribed after full assessment and diagnosis and MDT review.
    - Ensure weekly contact for at least the first four weeks. Assess for the emergence of adverse side effects such as anxiety, irritability, hostility, suicidal thoughts or self-harm.

- Inform the patient and their parents/carers of these potential adverse effects and urge them to contact the prescribing doctor if they emerge.
- Written and verbal information should be provided. This should also include details of delay in onset of effect, time course of treatment, the need to take medication as prescribed and the need to discontinue gradually at the end of treatment
- Start with 10mg per day as liquid Fluoxetine. This comes as 20mg/5ml. Then increase the dose after one week to 20mg capsules.

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- If fluoxetine is unsuccessful after an adequate trial at adequate doses and the depression is sufficiently severe to justify the trial of another antidepressant, NICE recommends citalopram or sertraline as second line treatment options.
- Starting doses should be low.
- Prozac brand of fluoxetine is the only licensed product for the treatment in the over 8 years old. No other treatment is licensed under the age of 18. Patients and parents/carers should be informed of the implications of this, and formal consent obtained.
- Do not use paroxetine or venlafaxine, tricyclic antidepressants or St John's Wort.
- Other antidepressant should start with half the daily adult starting dose. Increase if necessary over 2-4 weeks to the usual daily adult dose.
- There is little evidence regarding the effectiveness of doses above 20mg daily for fluoxetine or upper adult daily doses for other antidepressants.
- Higher doses should only be considered in older children of higher body weight and young people when the severity of the illness makes an early clinical response a priority.

5.2 Pregnancy

- The risks of medicine should be balanced against the risks of symptom relapse. Uncontrolled symptoms may affect the mother child relationship directly or via an increase in risk taking, such as co-morbid alcohol, drug and nicotine use.
- Risks associated with use of medicine to treat depression during pregnancy include, teratogenicity and neonatal side effects. The latter may be toxicity or withdrawal effects (usually mild and self-limiting). Little is known about the developmental effects of foetal exposure to antidepressants.
- With all woman of childbearing potential discuss contraception and the risks of symptom relapse and the use of medication in pregnancy.
- Most of the danger for organ damage is in weeks 3 to 8 post conception. This may be before a woman is aware she is pregnant. All woman of child bearing age should be advised of the importance of effective contraception. The woman should be encouraged to plan any pregnancies with the psychiatrist or other clinician.
- Treatment options will depend on the patient's previous history and the patient and clinicians preferences. These may include non-pharmacological treatments such as cognitive behavioural therapy, treatment break during the first trimester, continuing current effective treatment with monitoring or reducing or stopping treatment before delivery. Consult tests such as NICE, Drugs in Pregnancy, Maudsley prescribing guidelines. You can also contact the Trust Pharmacy Services (01302 798308) and/or the National Teratology information Service (0191 2321525).
- It is important to ensure all healthcare professionals involved in the pregnancy and delivery, are aware of any prescribed medicines.
- Exposure to SSRIs and SNRIs in late pregnancy may increase the risk of persistent pulmonary hypertension of the newborn.
- NICE recommends that paroxetine is stopped if a woman is planning a pregnancy or has an unplanned pregnancy.
- Venlafaxine may be associated with increased risk of high blood pressure at high doses.
- The choice of antidepressant may also be influenced by the woman's intention or not to breast feed.

6. Antidepressants and driving

- Section 4 of the Road Traffic Act 1988 does not differentiate between illicit or prescribed drugs. Therefore, any person who is driving or attempting to drive on the public highway or other public place whilst unfit due to any drug is liable for prosecution.
- All drugs action on the central nervous system can impair alertness, concentration and driving performance. This is particularly so at initiation of treatment, or soon after and when dosage is being increased. Driving must cease if adversely affected.
- The older tricyclic antidepressants can have pronounced anticholinergic and antihistaminic effects, which may impair driving. The more modern antidepressants may have fewer adverse effects. **These considerations need to be taken into account when planning the treatment of a patient who is a professional driver.**
- Anti-psychotic drugs, including the depot preparations, can cause motor or extrapyramidal effects as well as sedation or poor concentration, which may either alone or in combination be sufficient to impair driving. Careful clinical assessment is required.
- The epileptogenic potential of psychotropic medication should be considered particularly when patients are professional drivers.
- Benzodiazepines are the most likely psychotropic medication to impair driving performance, particularly the long acting compounds. **Alcohol will potentiate the effects.**
- Doctors have a duty of care to advise their patients of the potential dangers of adverse effects from medication and interactions with other substances, especially alcohol.

7. References

1. NICE Clinical Guideline (CG90) Depression: the treatment and management of depression in adults (update). http://guidance.nice.org.uk/CG90/Guidance/pdf/English
2. NICE Clinical Guideline (CG91) Depression in adults with a chronic physical health problem: Treatment and management. http://guidance.nice.org.uk/CG91/Guidance

3. BAP Consensus Guidelines. Evidence based guidelines for treating depressive disorder eith Antidepressants. http://www.bap.org.uk/pdfs/antidepressants.pdf
4. BNFonline (British Medical Association and the Royal Pharmaceutical Society of Great Britain). Online BNF at: www.bnf.org
5. Martindale – The complete drug reference online at: http://www.medicinescomplete.com/mc/ [subscription required]
6. SPC for all the drugs referred to in this guideline can be found in the Electronic Medicines Compendium (http://emc.medicines.org.uk/).

7. Psychotropic Drug Directory Bazire 2012
8. The Maudsley Guidelines 11th edition and online at http://www.library.nhs.uk/booksandjournals/ebooks/
9. SWY Depression guidelines
10. DVLA **For medical practitioners** At a glance guide to the current medical standards of fitness to drive Nov 2014 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/390134/aagv1.pdf
11. NICE Clinical guideline (CG 192) Antenatal and postnatal mental health: clinical management and service guidance https://www.nice.org.uk/guidance/cg192
12. NICE Clinical Guideline (CG28) Depression in children and young people: Identification and management in primary, community and secondary care http://www.nice.org.uk/guidance/cg28

Table 1: PHARMACOLOGICAL TREATMENTS FOR DEPRESSION
1a: FIRST AND SECOND LINE OPTIONS

First Line:	Relative Cost	Notes
Citalopram	**£**	Has less drug/drug interactions, but be aware of MHRA advice regarding dose related QTc prolongation
Sertraline	**£**	Sertraline has a superior tolerability and is preferred in cardiac disease
Mirtazapine	**£**	Useful where weight is not a concern and sedation is preferable Lack of anticholinergic side effects, lack of sexual side effects
Fluoxetine Liquid	**£** **££**	Long half life – useful if compliance is an issue, has many drug interactions
Second Line:	**Relative Cost**	**Notes consider if first line inappropriate or already tried**
Venlafaxine XL	£- ££	More toxic than SSRIs; risk of discontinuation reaction, avoid in uncontrolled hypertension
Lofepramine	££	Least cardiotoxic of TCAs
Trazodone	£	Useful in anxiety and agitation where sedation is required
Duloxetine	££	Little or no advantages over other antidepressants; Expensive; care needed to use correct dosage regimen; associated with nausea and headache, and can also increase blood pressure. It may however be considered in patients who also have co-morbid neuropathic pain
Reboxetine	**££**	Unlicensed in elderly patients, may be useful in patients who are sensitive to serotenergic side effects
Third Line:	**Reltive Cost**	Notes
Vortioxetine	**££**	Consider as an option if a patient has failed to respond to two different agents within a single episode of depression

1b: FOR SPECIALIST CARE INITIATION

Specialist Care initiation only	Relative Cost	Notes
MAOI's	**£**	Dietary problems. Use for atypical depression when lack of response to other antidepressants
Mianserin	**££**	Regular blood counts needed
Clomipramine	**£**	Useful if OCD symptoms are present as well
Tricyclics (other than those listed above)	**£**	Toxic in overdose, poorly tolerated

1c: NOT RECOMMENDED

Not Recommended		Notes
Dosulepin	£	Avoid due to increased cardiac risk and toxicity in overdose.
Agomelatine	£££	Liver function test required during use; expensive; Use not recommended by Trust. However if patients are admitted to our service on this medication, the prescriber must ensure that the recommended Liver Function Tests are carried out. https://www.gov.uk/drug-safety-update/agomelatine-valdoxan-risk-of-liver-toxicity

TABLE 2 :TREATMENT RESISTANT DEPRESSION

For initiation and stabilisation in secondary care

General Guidance on options
General guidance • Assure compliance, and manage ADR's that may impact on this • Escalate antidepressant doses for an adequate duration • Switch drugs – ensuring that all drug classes have been tried optimally • Augment the antidepressant with other drugs or combine two antidepressants Treatment Options • Use combination of mirtazapine & venlafaxine – recommended by NICE • Add lithium – well established – recommended by NICE • High Dose Venlafaxine >225mg/day (non-MR preparation up to 375mg, notes increased risk of side effects) • Augment with an antipsychotic if evidence of psychosis • If the above are unsuccessful, then consult current literature and seek expert opinion where necessary

Augmentation	Relative Cost	Notes (initiated in secondary care)
Lithium	£	Use in treatment resistant depression – blood tests needed
Antipsychotic	£-£££	Use in depression with psychotic symptoms or resistant major depression (see Maudsley Guidelines)

TABLE 3: USUAL RECOMMENDED TREATMENT OF DEPRESSION IN CHRONIC MEDICAL CONDITIONS

Co-morbidity	Recommended treatment In all chronic conditions any possible drug interactions must be considered as a matter of priority
Post stroke	• SSRIs • Mirtazapine (small effect on INR – causing an increase to INR)
Diabetes	• SSRIs – fluoxetine best supported by data • Venlafaxine • Mirtazapine
Cardiovascular disease	• SSRIs – preferably sertraline especially if also prescribed flecainide, propafenone. – not recommended if also prescribed antiplatelets, aspirin or anticoagulants due to increased risk of bleeding • Mirtazapine
Epilepsy	• Check choices with Medicines Information before use of any antidepressant
Hepatic	• Lofepramine or Paroxetine, monitor closely for increased side effects
Elderly	• SSRIs • Mirtazapine • In Parkinson's disease do not use SSRIs with MAO-B inhibitors e.g. selegiline
Renal impairment	• If unsure check with pharmacy before use of any antidepressant, especially if CKD 3b or worse
Musculoskeletal disease	• SSRIs not recommended to be used with NSAIDs. If essential use a gastroprotective agent at the same time
Migraine	• In people receiving triptans use mirtazapine / trazodone / mianserin or reboxetine

TABLE 4: RELATIVE SIDE-EFFECT PROFILES OF ANTIDEPRESSANTS

	MAIN SIDE EFFECTS					
Drug	**Drowsiness**	**Weight gain**	**Nausea**	**Anticholinergic effects**	**Sexual problems**	**Cardiac effects**
Citalopram	+	+	+++	+	+++	+
Sertraline	+	+	+++	+	+++	+
Fluoxetine	+	+	+++	+	+++	+
Escitalopram	+	+	+++	+	+++	+
Mirtazapine	+++	+++	o	o	o	+
Venlafaxine	+	+	+++	++	+++	++
Moclobemide	+	+	++	++	+	++
Amitriptyline	+++	++	++	+++	++	+++
Clomipramine	+++	++	++	+++	++	+++
Imipramine	++	++	++	++	++	+++
Nortriptyline	++	++	++	++	++	+++
Lofepramine	++	++	++	+	++	+++
Trazodone	+++	+	++	o	+	+++
Paroxetine	+	+	+++	+	+++	+
Fluvoxamine	+	+	+++	+	+++	+
Reboxetine	o	o	o	+++	+	++
Duloxetine	+	+	+++	++	+++	++
Phenelzine	+	+	++	++	++	+++
Agomelatine	o	o	o	o	o	++
Tryptophan	+	o	+	o	o	+
Lithium	+	++	+	o	o	+

TABLE 5: ADVICE ON SWITCHING ANTIDEPRESSANTS
(Adapted from the Maudsley Prescribing Guidelines)

From	To	Advice
MAOI's	anything	Stop and wait two weeks before initiating
Tricyclic Antidepressants (TCA)	MAOI	Withdraw and wait one week
	Other TCA	Cross taper cautiously
	Mirtazapine	Cross taper cautiously
	SSRI's	Halve dose, add SSRI and withdraw slowly
	Venlafaxine	Cross taper cautiously, start with venlafaxine 37.5mg
	Duloxetine	Cross taper cautiously, start with 60mg alternate days
SSRI's (except fluoxetine)	MAOI's	Withdraw and wait 2 weeks
	TCA	Cross taper cautiously with low dose TCA
	Mirtazapine	Cross taper cautiously
	Other SSRI	Withdraw and start new agent
	Venlafaxine	Cross taper cautiously and start venlafaxine 37.5mg at night
	Duloxetine	Withdraw, start 60mg on alternate days, increase slowly
Fluoxetine	MAOI's	Withdraw and wait 5-6 weeks
	TCA	Withdraw, wait 5-7 days, then slowly titrate cautiously
	Mirtazapine	Cross taper cautiously
	Venlafaxine	Withdraw, start 37.5mg at night an titrate slowly
	Duloxetine	Withdraw, wait 5-7 days, start 60mg on alternate days, increase slowly
Mirtazapine	MAOI	Withdraw, wait one week
	TCA	Withdraw, then start TCA
	SSRI/Venlafaxine	Cross taper cautiously
	Duloxetine	Withdraw, start 60mg on alternate days, increase slowly
Venlafaxine	MAOI	Withdraw and wait at least one week
	TCA/SSRI	Cross taper cautiously starting with low dose
	Mirtazapine	Cross taper cautiously
	Duloxetine	Withdraw, start 60mg on alternate days, increase slowly
Duloxetine	MAOI	Withdraw and wait one week
	TCA	Cross taper cautiously starting with low dose
	SSRI/Venlafaxine and Duloxetine	Withdraw then start new drug